9nc

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,972	01/04/2002	Jeffrey S. Bartlett	28335/36996US	9566

4743 7590 08/11/2004

MARSHALL, GERSTEIN & BORUN LLP
6300 SEARS TOWER
233 S. WACKER DRIVE
CHICAGO, IL 60606

EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/038,972	BARTLETT, JEFFREY S.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,17,18 and 21-40* is/are pending in the application.

4a) Of the above claim(s) *27-40* is/are withdrawn from consideration.

5)☒ Claim(s) *24* is/are allowed.

6)☒ Claim(s) *1-10,17,18,21-23,25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to an amendment and a Declaration under 37 CFR 1.132 by Dr. Jeffrey Bartlett filed 5/27/04. The Declaration has been considered. Claims 11-16, 19-20 and 41 have been cancelled. Claims 1-10, 17-18 and 21-40 are pending in this application. Claims 27-40 have been withdrawn. Claims 17 and 21-25 have been amended. Claims 1-10, 17-18, 21-26 are examined herein.

Information Disclosure Statement

An IDS filed 6/17/04 has been identified and the documents considered. The signed and initialed PTO Form 1449 has been mailed with this action.

Claim Objections

Upon reconsideration, claims 21-23 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiply dependent claim. See MPEP § 608.01(n). This objection has been made but the claims are treated on the merits in this office action as the claims have been found rejected in an office action mailed 12/24/03.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 17-18, 21-23 and 25-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an AAV2 vector with an amino acid insertion following amino acids 139, 161, 459, 584, 588 and 657, does not reasonably provide enablement for ANY AAV vector other than AAV2 with insertions at corresponding sites. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record in the office action mailed 12/24/03.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) Nature of invention. The invention recites an AAV vector comprising a capsid protein with an amino acid insertion in the capsid. Claim 10 recites that the amino acid insertion can be a targeting peptide such as CDCRGDCFC (SEQ ID NO 10). This invention requires a complex combination of molecular cloning and viral and cell culture techniques to generate the recombinant adenovirus.

2) Scope of the invention. The invention recites very specific sites for insertion of the amino acid i.e. following the amino acid in positions 139, 161, 459, 584, 588 and 657 in SEQ ID NO:13 which is VP1 protein. These sites are based upon AAV2 as a

reference sequence. However, the recitation of an insertion amino acid in corresponding sequences from any AAV exacerbates a complex method.

3) Number of working examples and guidance. The instant specification teaches means of constructing and analyzing a recombinant AAV2 vector with amino acid insertions following amino acids 139, 161, 459, 584, 588 and 657. As guidance, applicants teach that sites for insertion can be surface and secondary structural regions that were identified in a comparison of five parvoviruses. Following this, site-directed mutagenesis of AAV2 was used to identify specific sites by insertion mutagenesis (see example 1, page 11-12). Applicants teach that corresponding sites in other parvovirus can be extrapolated to the sites identified in AAV2 (see e.g. page 4, line 3-12).

4) State of the art. There has been much interest in the development of viruses that transduce therapeutic genes into specific target tissues. Manipulation of AAV for altered tropism is a new and developing art.

5) Unpredictability of the art. Chiorini et al teach the relationship of AAV4 and AAV3 to AAV2 (Journal of Virology, 1997 see Figure 3 and page 6828, column 2). The relationships between AAV2 and the capsid proteins of AAV3 and AAV2 are 62% and 63% respectively and to Moscovy duck and goose capsid proteins the homology is 53%. The homology to other autonomous parvovirus is quite low (page 6828, column 2, paragraph 3,line 1-7).

6) Amount of Experimentation Required. The invention recites an AAV vector comprised of an amino acid insertion following amino acids 139, 161, 459, 584, 588 and 657 of AAV2. In view of the unpredictability of the art of identifying the same sites in any other AAV vector: undue experimentation would be required to practice the claimed

methods with reasonable expectation of success, absent a specific and detailed description in the specification. The level of skill in the art covering this invention was high at the time of invention; however, given the unpredictability of the art, the poorly developed state of the art, the lack of working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue experimentation to practice the claimed invention.

Response to Amendment- 112 first paragraph, lack of enablement

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph on pages 6-7 of the amendment filed 5/27/04. Applicants arguments are based upon the arguments presented in a 1.132 Declaration by Dr. Jeffrey Bartlett filed 5/27/04. Essentially the arguments presented in the Declaration and summarized on pages 6-9 of the amendment filed 5/27/04 are the following. 1) The genetic structure and primary amino acid structure of the known AAV serotypes are similar and areas of variation are localized to corresponding regions of the capsid proteins. While the percentage of amino acid identity is not striking, the biological similarity is significant. The relative location of loops and sites of epitope insertion in relation to the invariant regions that comprise the core is essential. 2) A stated in the specification, three-dimensional structural analysis of five parvovirus was available at the time of filing and that of VP3 is similar among these virions. Furthermore, three-dimensional structural analysis could have been carried out for other AAV vectors. 3) Three-dimensional analysis of AAV2 VP3 was performed using Chou-Fasman and Garnier-Robson and this analysis is presented in comparison to the actual secondary structure based upon crystal structure. Furthermore, computer

modeled secondary structure based upon this is presented for AAV3, AAV4 and AAV5 and the location of insertion sites could have been predicted. 4) Epitope insertion experiments were carried out on various AAV serotypes using a biotin acceptor plasmid (BAP) insertion sequence into VP1 between amino acids 584 and 588. No disruption of particle formation resulted. Therefore applications conclude that epitope insertions at sites in various AAV vector serotypes can be made according to the instant invention.

The Declaration under 37 CFR 1.132 filed 5/27/04 and the amendment filed 5/27/04 have been fully considered but they are not persuasive. The instant invention does not teach means of identifying "corresponding sequences" in any AAV such that the recited AAV vector can be made. Specifically, the instant specification teaches the identification of regions of AAV2 regions that are exposed on the surface of the virion and can be replaced (page 11, line 6-12). Following comparison of AAV2 with structural information from five known parvoviruses, 19 regions of VP1 were identified as potential targets for insertional mutagenesis. Of these six sites were classified as type III mutants, which are mutants that produce fully infectious virions. Absent evidence to the contrary, there is undue experimentation to determine the relevant "corresponding sites" in any other AAV serotype. Applicants have provided evidence in a Declaration that VP3 protein from known parvoviruses was similar to AAV2 VP3 three-dimensional models. The AAV2 VP3 model was generated post-filing. It does appear from a comparison of the AAV2 proposed model and the solved model that a region that did not resolve well (figure 2B) is ultimately the location of multiple insertion sites (see figure 5). Hence the actual usefulness of modeling for identifying these insertion is unclear. It

appears that insertional mutagenesis was required to identify insertion sites between amino acids 443 and 637.

Ultimately, any successes recited in the Declaration cannot be extrapolated back to the instant invention because the instant specification lacks support for the teachings of the Declaration. The Declaration teaches one how to identify VP3 loop structures by comparison of sequences between AAV2 and parvovirus. Subsequently, the Declaration teaches that these loop structures can be potentially extrapolated to AAV1, AAV3, AAV4 and AAV5. This does not provide the guidance or the information necessary to identify the recited sites in AAV VP1 protein. Comparatively, the structure of VP1 is dissimilar to VP3 but is similar to VP2. Kronenberg et al have superimposed empty capsids of AAV2 to three-dimensional structure of CPV. In this analysis, the outer surface which is comprised of VP1 and VP2 was found to be dissimilar between the two (see page 999, column 1, paragraph 1 and figure 4). Therefore, it is unpredictable that modeling of VP1 using parvovirus would generate the same kind of model system detailed for VP3. Combined with the lack of sequence homology between AAV serotypes in VP1, the lack of guidance in the specification, undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification.

Claims 1-10, 17-18 and 21-23 and 25-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in the office action mailed 12/24/03.**

Applicants claim an AAV vector with an amino acid insertion at specific amino acid sequences with a critical element that peptides or polypeptides of interest may be inserted for presentation in a desired conformation to allow for the development of AAV vectors that deliver DNA to specific target cells or display surface immunogenic peptides or polypeptides (see e.g. page 3,line 18-22).

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

In the instant invention, applicants recite that these sites are in positions following amino acids 139, 161, 459, 584, 588 or 657 in the VP1 capsid which sequence is presented in SEQ ID NO 13. This sequence corresponds to VP1 of AAV2. Applicants teach that surface and secondary structural regions were identified in a comparison of five parvoviruses. However, this broad and hypothetical functional characteristic was not used to identify the specific sites of AAV that could tolerate insertion mutagenesis and provide for presentation of peptides for targeting or immunogen presentation. Rather site-directed mutagenesis of AAV2 was used to identify the specific sites of insertion was not used to identify the regions of insertion (see example 1, page 11-12). However, the

structural requirements of these regions to meet the functional limitations of the claimed invention are unknown. Applicants teach that these sites can be understood to be corresponding sites in other parvovirus (see e.g. page 4, line 3-12). Neither applicant nor the prior art provide a correlation between the structure of any parvovirus VP1 protein and the functional requirements for identification of sites for insertion of a peptide for representation of targeting motifs or immunogens. Chiorini et al teach the relationship of AAV4 and AAV3 to AAV2 (Journal of Virology, 1997 see Figure 3 and page 6828, column 2). The relationships between the capsid proteins are 62% and 63% and to Moscovy duck and goose 53% homology while to other autonomous parvovirus there is little homology (page 6828, column 2, paragraph 3,line 1-7). It is unclear what functional characteristics should be used to identify the sites of insertion for vectors other than AAV2. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus. Given the diversity of parvovirus capsid regions and the lack of written disclosure of the structural characteristics, and the lack of written disclosure of the functional characteristics required for the insertion sites to be identified in other parvovirus, it is concluded that applicant was not in possession of their invention.

Response to Amendment- 112 first paragraph, lack of written description

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph on pages 8-9 of the amendment filed 5/27/04. Applicants argue essentially the following. 1) The predicted secondary structures of the known AAV serotypes are similar and hence similar regions of the capsid proteins are exposed. Thus one of skill in the art would

understand the specification describes the genus of AAV vectors recited in the claims. 2) The identification of exposed loops satisfies the requirement for structural characteristics of the AAV insertion sites. 3) The potential of computer modeling and use of programs that predict secondary structure were available at the time of filing.

Applicants' arguments filed 5/27/04 have been fully considered but they are not persuasive. The disclosure of AAV2 insertion sites does not constitute written description for the identification of any insertion sites in any AAV serotype. The skilled artisan cannot envision the detailed structure of the broad class of AAV serotype insertion sites regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that the protein is part of the invention and a reference to a potential method for isolating it. The disclosure of a single member of this genus does not suggest that the applicant was in possession of the genus.

Conclusion

Claim 24 is allowed.

Claims 1-10, 17-18, 21-23 and 25-26 are rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

August 3, 2004

GERRY LEFFERS
PRIMARY EXAMINER